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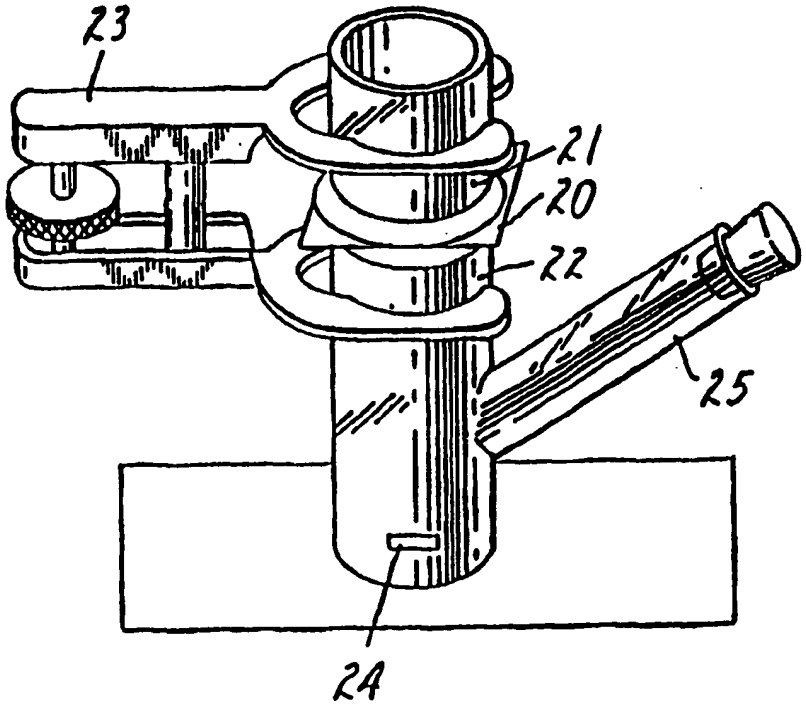
(54) Title: TRANSDERMAL ANTIINFLAMMATORY COMPOSITION

(57) Abstract

Transdermal drug formulations containing a nonsteroidal antiinflammatory drug, a lipophilic excipient, and a hydrophilic excipient. The drug is substantially fully dissolved in the formulation, and the excipients are miscible with one another in the amounts employed.



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TRANSDERMAL ANTIINFLAMMATORY COMPOSITION

Background of the Invention

Field of the Invention

This invention relates to topical and transdermal drug formulations. In another aspect this invention relates to formulations containing nonsteroidal antiinflammatory drugs.

Description of the Related Art

Topical and transdermal drug formulations are designed to deliver a therapeutically effective amount of drug to or across the skin of a patient. Devices known to the art include reservoir type devices involving membranes that control the rate of drug release to the skin, gels and creams, and devices involving a dispersion of the drug in a matrix such as a pressure sensitive adhesive. As the skin presents a barrier to the drug it is often desirable or necessary to incorporate certain materials that enhance the rate at which the drug passes through the skin. For any particular drug, however, the type of device, the transdermal flux rate that is suitable, and suitable formulation components are dependent upon the particular drug to be delivered.

Nonsteroidal antiinflammatory drugs (NSAIDS) are commonly used as analgesic, antipyretic, and antiinflammatory treatments. Oral dosage forms are most common. However, sustained use of oral NSAIDS is known to cause peptic ulcers. Accordingly it is sometimes desirable to administer such drugs in a manner that avoids the gastrointestinal tract. Transdermal administration is one such route. However, in order for a transdermal formulation to be effective

and suitable for general use by patients it is desirable that the formulation have a high transdermal flux rate, allowing a therapeutically effective blood level of the drug to be achieved or maintained when the formulation is applied to a relatively small area of the skin.

Summary of the Invention

This invention provides a substantially non-aqueous topical and/or transdermal drug delivery formulation, comprising:

(i) a therapeutically effective amount of a nonsteroidal antiinflammatory drug selected from the group consisting of phenylpropionic acid derivatives and phenylacetic acid derivatives;

(ii) a lipophilic excipient selected from the group consisting of fatty acid alkyl esters and fatty acid monoglycerides; and

(iii) a hydrophilic excipient selected from the group consisting of polyethylene glycols, polyethylene glycol esters, isosorbide ethers, and diethylene glycol ethers,

wherein the lipophilic excipient and the hydrophilic excipient are miscible with one another in the amounts employed, and wherein the nonsteroidal antiinflammatory drug is substantially fully dissolved in the formulation.

This invention also provides a topical and/or transdermal formulation as described above, wherein the formulation further comprises a pressure sensitive adhesive and wherein the drug, the lipophilic excipient, and the hydrophilic excipient are substantially uniformly dispersed or preferably dissolved in the pressure sensitive adhesive.

This invention also provides a topical and/or transdermal drug delivery formulation, comprising:

(i) a therapeutically effective amount of a nonsteroidal antiinflammatory drug selected from the group consisting of phenylpropionic acid derivatives and phenylacetic acid derivatives;

(ii) a lipophilic excipient selected from the group consisting of ethyl oleate, isopropyl myristate, and a mixture thereof; and

(iii) dimethylisosorbide,

wherein the lipophilic excipient and the dimethylisosorbide are miscible with one another in the amounts employed, and wherein the nonsteroidal antiinflammatory drug is substantially fully dissolved in the formulation.

This invention also provides a topical and/or transdermal drug delivery formulation, comprising:

(i) a therapeutically effective amount of a nonsteroidal antiinflammatory drug selected from the group consisting of phenylpropionic acid derivatives and phenylacetic acid derivatives;

(ii) a lipophilic excipient selected from the group consisting of fatty acid alkyl esters and fatty acid monoglycerides;

(iii) a hydrophilic excipient selected from the group consisting of polyethylene glycols, polyethylene glycol esters, isosorbide ethers, and diethylene glycol ethers; and

(iv) a pressure sensitive adhesive,

wherein the drug, the lipophilic excipient, and the hydrophilic excipient are substantially uniformly dispersed or preferably dissolved in the pressure sensitive adhesive.

This invention also provides an adhesive coated sheet material comprising a flexible backing bearing on one surface thereof a formulation comprising a homogeneous mixture of

(i) a pressure sensitive adhesive;

(ii) a therapeutically effective amount of a nonsteroidal antiinflammatory drug selected from the group consisting of phenylpropionic acid derivatives and phenylacetic acid derivatives;

(iii) a lipophilic excipient selected from the group consisting of fatty acid alkyl esters and fatty acid monoglycerides; and

(iv) a hydrophilic excipient selected from the group consisting of polyethylene glycols, polyethylene glycol esters, isosorbide ethers, and diethylene glycol ethers.

This invention also provides a method of treating in an animal a condition capable of treatment by a nonsteroidal antiinflammatory drug, comprising the steps of:

(i) providing a formulation as described above;

(ii) applying the formulation to the skin of the animal; and

(iii) allowing the formulation to remain on the skin in order to establish or maintain a therapeutically effective blood level of the nonsteroidal antiinflammatory drug.

The combination of excipients defined above has been found to afford particularly high transdermal flux rates of the nonsteroidal antiinflammatory drugs.

Brief Description of the Drawing

The drawing shows a perspective view of a diffusion cell used to determine transdermal flux of a formulation of the invention.

Detailed Description of the Invention

The formulations of the invention contain a nonsteroidal antiinflammatory drug. This class of drugs is well known to those skilled in the art and includes phenylpropionic acid derivatives (e.g., fenoprofen, ibuprofen, flurbiprofen, ketoprofen, and

naproxen) and phenylacetic acid derivatives (e.g., 4-biphenylacetic acid, ibufenac). Preferred NSAIDs for use in this invention include phenylpropionic acid derivatives. The most preferred propionic acid derivative is flurbiprofen, especially S(+) flurbiprofen.

The nonsteroidal antiinflammatory drug is present in a formulation of the invention in a therapeutically effective amount. The amount that constitutes a therapeutically effective amount varies according to the particular drug to be delivered, the indication to be treated, the surface area of the skin over which the formulation is to be placed, and on the other components of the formulation. Accordingly it is not practical to enumerate particular preferred amounts but such can be readily determined by those skilled in the art with due consideration of these factors. Generally, however, the nonsteroidal antiinflammatory drug is preferably present in an amount of about 1 to about 25 percent, preferably about 5 to about 15 percent, by weight based on the total weight of the formulation.

The terms "hydrophilic" and "lipophilic" as used herein refer to relative hydrophilicity/lipophilicity as measured on the hydrophile-lipophile balance (HLB) scale (see, e.g., pages 304-306, Remington's Pharmaceutical Sciences, 18th Edition, 1990, A. R. Gennaro, Ed., Mack Publishing Company, Easton, Pennsylvania, Griffin, W. C., J. Soc. Cos. Chem. 1949, 1, 311, and Griffin, W. C., J. Soc. Cos. Chem. 1954, 5, 249). Preferably, hydrophilic excipients have an HLB of at least about 10, while lipophilic excipients have an HLB of less than about 10.

The formulations of the invention contain a lipophilic excipient. Suitable lipophilic excipients include fatty acid alkyl esters, preferably alkyl esters of C_8-C_{22} fatty acids, more preferably alkyl

esters of C_{12}-C_{18} fatty acids. Lower alkyl esters (lower alkyl as used herein means straight chain or branched chain alkyl containing one to four carbon atoms) such as ethyl oleate, isopropyl palmitate, and isopropyl myristate are preferred. Fatty acid monoglycerides (e.g., glycerol monolaurate) are also suitable.

The formulations of the invention also contain a hydrophilic excipient. Preferably the drug used in the formulation has a solubility in this excipient of at least about 200 mg/g, more preferably at least about 300 mg/g, most preferably at least about 350 mg/g. Suitable hydrophilic excipients include polyethylene glycols (e.g., PEG 400) and esters thereof such as PEG 400 monolaurate, isosorbide ethers such as isosorbide dimethyl ether, and diethylene glycol ethers such as diglyme, diethylene glycol diethyl ether, and diethylene glycol dibutyl ether.

The formulations of the invention can contain one or more excipients from each of the above described classes. The hydrophilic excipient can be present in any ratio relative to the lipophilic excipient. It is preferred that the hydrophilic excipient be present in an amount of about 10 to about 1000 parts by weight, preferably about 100 parts by weight, based on 100 parts by weight of the lipophilic excipient. The total excipient (hydrophilic and lipophilic combined) is preferably present in an amount of about 25 to about 5000, more preferably about 50 to about 1000, parts by weight based on 100 parts by weight of the drug. It is generally preferred that a formulation of the invention exhibit a relatively high flux rate, and certain combinations of excipients will be found to be preferable when used in connection with certain drugs.

A particularly preferred formulation of the invention involves flurbiprofen as the nonsteroidal antiinflammatory drug and a lipophilic excipient including isopropyl myristate, ethyl oleate, or both,

and including dimethyl isosorbide as the hydrophilic excipient. The lipophilic excipient can contain a combination of isopropyl myristate and ethyl oleate in any ratio, preferably in a ratio of about 2:1 to 1:2. The hydrophilic excipient dimethyl isosorbide is preferably present in an amount of about 10 to about 1000 parts by weight, preferably about 100 parts by weight, based on 100 parts by weight of the weight of the lipophilic excipient.

The formulations of the invention can be used as solutions containing essentially only the drug, the lipophilic excipient, and the hydrophilic excipient. Preferably they contain further components, such as those that form a matrix for the drug, the lipophilic excipient, and the hydrophilic excipient. A preferred matrix for use in a formulation of the invention is a pressure sensitive adhesive. In such an embodiment the pressure sensitive adhesive preferably constitutes from about 60 to about 80 percent by weight based on the total weight of the formulation; the hydrophilic excipient preferably constitutes from 5 to 15 percent by weight based on the total weight of the formulation, the lipophilic excipient preferably constitutes about 5 to 15 percent by weight based on the total weight of the formulation, and the drug preferably constitutes 1 to about 25 percent by weight based on the total weight of the formulation.

Suitable pressure sensitive adhesives include acrylic polymers and polyisobutylene pressure sensitive adhesives. Particularly preferred acrylic polymers include acrylic adhesives that contain, as a major constituent (i.e., at least about 80 percent by weight of all monomers in the polymer), a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms. Examples of suitable monomers are those discussed below in connection with the "A Monomer".

These adhesives can further contain minor amounts of other monomers such as the "B Monomers" listed below.

Preferred adhesives include acrylic pressure sensitive adhesive copolymers containing A and B Monomers as follows: Monomer A is a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms, preferably 6 to 10 carbon atoms, more preferably 6 to 8 carbon atoms, and most preferably 8 carbon atoms. Examples of suitable A Monomers are n-butyl, n-pentyl, n-hexyl, isoheptyl, n-nonyl, n-decyl, isohexyl, 2-ethyloctyl, isooctyl and 2-ethylhexyl acrylates. The most preferred A Monomer is isooctyl acrylate.

Monomer B is a reinforcing monomer selected from the group consisting of acrylic acid; methacrylic acid; alkyl acrylates and methacrylates containing 1 to 3 carbon atoms in the alkyl group; acrylamide; methacrylamide; lower alkyl-substituted acrylamides (i.e., the alkyl group containing 1 to 4 carbon atoms) such as tertiary-butyl acrylamide; diacetone acrylamide; n-vinyl-2-pyrrolidone; vinyl ethers such as vinyl tertiary-butyl ether; substituted ethylenes such as derivatives of maleic anhydride, dimethyl itaconate and monoethyl formate and vinyl perfluoro-n-butyrate. The preferred B Monomers are acrylic acid, methacrylic acid, the above described alkyl acrylates and methacrylates, acrylamide, methacrylamide, and the above described lower alkyl substituted acrylamides. The most preferred B Monomer is acrylamide.

In one embodiment of a pressure sensitive adhesive composition of the invention, the pressure sensitive adhesive copolymer containing A and B Monomers as set forth above preferably contains the A Monomer in an amount by weight of about 80 percent to about 98 percent of the total weight of all monomers in the copolymer. The A Monomer is more preferably present in an amount by weight of about 88 percent to about 98

percent, and is most preferably present in an amount by weight of about 91 percent to about 98 percent. The B Monomer in such a copolymer is preferably present in the pressure sensitive adhesive copolymer in an amount by weight of about 2 percent to about 20 percent, more preferably about 2 percent to about 12 percent, and most preferably 2 to 9 percent of the total weight of the monomers in the copolymer.

In another embodiment, the adhesive copolymer comprises about 60 to about 80 percent by weight (and preferably about 70 to about 80 percent by weight) of the above-mentioned hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol (i.e., Monomer A described above) based on the total weight of all monomers in the copolymer; about 4 to about 9 percent by weight based on the total weight of all monomers in the copolymer of a reinforcing monomer selected from the group consisting of acrylic acid, methacrylic acid, an alkyl acrylate or methacrylate containing 1 to 3 carbon atoms in the alkyl group, acrylamide, methacrylamide, a lower alkyl-substituted acrylamide, diacetone acrylamide and N-vinyl-2-pyrrolidone; and about 15 to about 35 percent by weight (and preferably about 15 to about 25 percent by weight) of vinyl acetate based on the total weight of all monomers in the copolymer. In this embodiment the preferred acrylic or methacrylic acid ester is isooctyl acrylate and the preferred reinforcing monomer is acrylamide.

The above described adhesive copolymers are known, and methods of preparation therefor are well known to those skilled in the art, having been described for example, in U.S. Patent RE 24,906 (Ulrich), the disclosure of which is incorporated herein by reference. The polymerization reaction can be carried out using a free radical initiator such as an organic peroxide (e.g., benzoylperoxide) or an organic azo

compound (e.g., 2,2'-azobis(2,4-dimethylpentane-nitrile), available under the trade designation "Vazo 52" from DuPont).

Since pressure sensitive adhesives such as those described above are inherently rubbery and tacky and are suitably heat and light stable, there is no need to add tackifiers or stabilizers. However, such can be added if desired.

Other conventional matrices are suitable for use in a formulation of the invention. For example, creams, gels, and ointment formulations are suitable. A cream formulation can contain conventional components including emollients (such as long chain alcohols, petrolatum, light mineral oil, or acetylated lanolin), emulsifiers (e.g., nonionic surfactants such as polysorbate 60 and sorbitan monostearate, aluminum stearate), thickeners (gums, long chain alcohols such as stearyl alcohol), and preservatives. An ointment formulation can contain a pharmaceutically acceptable ointment base such as petrolatum, and emollients, emulsifiers, and thickeners. Suitable amounts of the components of such matrices are readily selected by those skilled in the art.

A gel, cream, ointment, or solution formulation of the invention can be prepared using conventional methods, combining the drug, the lipophilic excipient, the hydrophilic excipient, and any other components in suitable amounts readily selected by those skilled in the art. It is preferred that the drug remain dissolved in the formulation in order that it is readily released from the formulation to the skin.

Adhesive coated sheet materials of the invention can be prepared by combining dry adhesive, drug, and the excipients with a suitable organic solvent (e.g., hexane, heptane, ethyl acetate, ethanol, or methanol, depending upon the particular adhesive used) to afford a coating solution. The total solids content of the

solution is preferably in the range of about 15 percent to about 40 percent, and more preferably in the range of about 20 to about 35 percent by weight, based on the total weight of the coating solution.

The coating solutions described above are preferably coated onto one surface of a suitable backing of sheet material, such as a film, to form a pressure sensitive adhesive coated sheet material. A pressure sensitive adhesive coated sheet material of the invention can be prepared by knife coating a suitable release liner to a predetermined uniform thickness with a wet adhesive formulation. This adhesive coated release liner is then dried and laminated onto a backing using conventional methods. Suitable release liners include conventional release liners comprising a known sheet material, such as a polyester web, a polyethylene web, or a polystyrene web, or polyethylene-coated paper, coated with a suitable silicone-type coating such as that available under the trade designation Daubert 164Z, from Daubert Co. The backing can be occlusive, non-occlusive or a breathable film as desired. The backing can be any of the conventional materials for pressure sensitive adhesive tapes, such as polyethylene, particularly low density polyethylene, linear low density polyethylene, high density polyethylene, randomly-oriented nylon fibers, polypropylene, ethylene-vinylacetate copolymer, polyurethane, rayon and the like. Backings that are layered, such as polyethylene-aluminum-polyethylene composites are also suitable. The backing should be substantially non-reactive with the ingredients of the formulation.

The adhesive coated sheet material of the invention can be made in the form of an article such as a tape, a patch, a sheet, a dressing or any other form known to those skilled in the art.

A formulation of the invention can be used to treat any condition capable of treatment with a nonsteroidal antiinflammatory drug, e.g., pain and inflammation associated with arthritis and soft tissue injury. The formulation can be incorporated in an appropriate device if necessary or desirable (e.g., in the case of a solution formulation it might be necessary or desirable to use a suitable reservoir device to contain the formulation). The formulation can then be placed on the skin and allowed to remain for a time sufficient to achieve or maintain the intended therapeutic effect. Drug delivery can be topical such that the drug has a local therapeutic effect or transdermal such that the drug has a systemic effect.

The examples set forth below are intended to illustrate the invention.

The following test methods have been employed in the examples which thereafter follow.

In Vitro Test Method

Although animal skins are known to give significant quantitative differences in drug penetrability as compared to human skin, a rank order correlation is generally observed with various drugs (M. J. Bartek and J. A. LaBudde in "Animal Models in Dermatology", H. Maibach, Ed., Churchill Livingstone, New York, 1975, pp. 103-119). Hairless mouse skin has been recommended as a readily available animal skin for use in diffusion cells with steroids and other small molecules (R. B. Stoughton, Arch. Derm., 99, 753 (1969), J. L. Cohen and R. B. Stoughton, J. Invest. Derm. 62, 507 (1974), R. B. Stoughton in "Animal Models in Dermatology", pp. 121-131). In the specific test procedure used herein, hairless mouse skin removed from female hairless mice that were 4-6 weeks old was used. The skin was maintained on ice until use, and it was

preferably used within 8 hours of sacrifice. The mouse skin was mounted on a diffusion cell of the type shown in the Drawing. The cell is modeled after those described in the literature, e.g., J. L. Cohen, R. B. Stoughton, J. Invest. Derm., 62, 507 (1974) and R. B. Stoughton, Arch. Derm., 99, 753 (1964). As shown in the Drawing, mouse skin 20 was mounted epidermal side up between upper portion 21 and lower portion 22 of the cell, which are held together by means of ball joint clamp 23.

The portion of the cell below the mounted skin was completely filled with receptor fluid (40% PEG 400 modified Ringer solution) such that the receptor fluid contacted the skin. The receptor fluid was stirred using magnetic stir bar 24 and a magnetic stirrer (not illustrated). The sampling port 25 was covered except when in use.

When a solution formulation was evaluated, the formulation was applied to the epidermal (upper) side of the skin to cover in an even layer only the area of the skin that would be in contact with the receptor fluid when the skin is mounted in the diffusion cell. When an adhesive coated sheet material was evaluated, the skin was mounted on the diffusion cell and a 1.77 cm^2 patch was applied to the skin and pressed to cause uniform contact to the skin. Generally, the formulation was applied to the skin prior to the time the receptor fluid was added to the cell below the skin.

The cell was then placed in a constant temperature (32 ± 2°C) chamber. To maintain constant temperature, the chamber utilized a heat exchanger coupled to a constant temperature bath, with a fan to circulate air. The receptor fluid was stirred by means of a magnetic stirring bar throughout the experiment to assure a uniform sample and a reduced diffusion barrier layer on the dermal side of the skin. The receptor fluid was

replaced at 3, 6, 9, 12, 19, and 24 hours. The withdrawn receptor fluid was analyzed for drug content by conventional high pressure liquid chromatography.

This in vitro method is referred to as the hairless mouse skin model. The values stated for skin penetration are the average of 3 independent determinations using a different mouse skin for each determination.

Solubility of a representative nonsteroidal antiinflammatory drug, flurbiprofen, in representative hydrophilic excipients was determined by a sequence of quantitative additions of drug to the respective excipient followed by stirring in a test tube for 24 h at 20°C. The data below show the drug content of a saturated solution.

Excipient	Drug Content (mg/g)
PEG 400 monolaurate	306.7
Dimethylisosorbide	403.9
PEG 400	425.8
Diethylene glycol dimethyl ether	544.6

A solution formulation of the invention was prepared by saturating a 1:1 mixture of dimethyl isosorbide (a hydrophilic excipient) and isopropyl myristate (a lipophilic excipient) with flurbiprofen. The solution was used in the Hairless Mouse Skin model described above. Three independent determinations gave cumulative drug release amounts of 12.18, 9.66, and 14.53 mg/24h/cm^2.

A solution formulation of the invention was prepared by saturating a 1:1 mixture of dimethyl isosorbide (a hydrophilic excipient) and ethyl oleate (a lipophilic excipient) with flurbiprofen. The solution was used in the Hairless Mouse Skin model

described above. Three independent determinations gave cumulative drug release amounts of 11.66, 4.77, and 10.43 mg/24h/cm^2.

Example 1

A formulation of the invention involving an acrylate based pressure sensitive adhesive matrix was prepared by dissolving the excipients (isopropyl myristate, 5.50 g, dimethyl isosorbide, 4.50 g), the drug [S(+) flurbiprofen, 4.00 g], and an adhesive [a 93:7 isooctylacrylate:acrylamide polymer (19.33 g), prepared according to the method set forth in Example 6 of U.S. Pat. No. 4,751,087 (Wick)] in an appropriate solvent (ethyl acetate, 61.68 g, and methanol, 6.85 g) to form a coating solution. The coating solution was coated out onto a transparent release liner (SCOTCHPAK™ 1022 liner, 3M) at a wet film thickness of 560 μm. The coating was dried for 2 min at 20°C and then at 45 min at 60°C. The coated release liner was laminated onto a polyethylene foam backing. The resulting device had a drug loading of 1.2 mg/cm^2.

A 1.77 cm^2 sample of the device was tested according to the Hairless Mouse Skin model set forth above. An identical sized sample of a commercially available flurbiprofen device (ADOFEED, Mikasa) having a drug loading of 0.3 mg/cm^2 was also tested. The device of the invention afforded a transdermal flux of 26.4 μg/cm^2/h, while the commercial device afforded a transdermal flux rate of 3.3 μg/cm^2/h.

CLAIMS:

1. A substantially non-aqueous topical and/or transdermal drug delivery formulation, comprising:

(i) a therapeutically effective amount of a nonsteroidal antiinflammatory drug selected from the group consisting of phenylpropionic acid derivatives and phenylacetic acid derivatives;

(ii) a lipophilic excipient selected from the group consisting of fatty acid alkyl esters and fatty acid monoglycerides; and

(iii) a hydrophilic excipient selected from the group consisting of polyethylene glycols, polyethylene glycol esters, isosorbide ethers, and diethylene glycol ethers,

wherein the lipophilic excipient and the hydrophilic excipient are miscible with one another in the amounts employed, and wherein the nonsteroidal antiinflammatory drug is substantially fully dissolved in the formulation.

2. A formulation according to Claim 1, wherein the formulation further comprises a pressure sensitive adhesive and wherein the drug, the lipophilic excipient, and the hydrophilic excipient are dissolved in the pressure sensitive adhesive.

3. A formulation according to Claim 1 wherein the nonsteroidal antiinflammatory drug is flurbiprofen.

4. A formulation according to Claim 1 wherein the nonsteroidal antiinflammatory drug is present in an amount of about 1 to about 25 percent by weight based on the total weight of the formulation.

5. A formulation according to Claim 1, wherein the lipophilic excipient is ethyl oleate, isopropyl

palmitate, isopropyl myristate, or glycerol monolaurate.

6. A formulation according to Claim 1, wherein the nonsteroidal antiinflammatory drug has a solubility in the hydrophilic excipient of at least about 200 mg/g.

7. A formulation according to Claim 1, wherein the hydrophilic excipient is PEG 400, PEG 400 monolaurate, isosorbide dimethyl ether, diglyme, diethylene glycol diethyl ether, or diethylene glycol dibutyl ether.

8. A formulation according to Claim 1, wherein the lipophilic excipient is isopropyl myristate, ethyl oleate, or a combination thereof.

9. A formulation according to Claim 1, wherein dimethyl isosorbide is the hydrophilic excipient.

10. A formulation according to Claim 3, wherein the lipophilic excipient is ethyl oleate, isopropyl palmitate, isopropyl myristate, or glycerol monolaurate.

11. A formulation according to Claim 3, wherein the flurbiprofen has a solubility in the hydrophilic excipient of at least about 200 mg/g.

12. A formulation according to Claim 3 wherein the flurbiprofen is present in an amount of about 1 to about 25 percent by weight based on the total weight of the formulation.

13. A formulation according to Claim 3, wherein the hydrophilic excipient is PEG 400, PEG 400

monolaurate, isosorbide dimethyl ether, diglyme, diethylene glycol diethyl ether, or diethylene glycol dibutyl ether.

14. A formulation according to Claim 3, wherein the lipophilic excipient is isopropyl myristate, ethyl oleate, or a combination thereof.

15. A formulation according to Claim 3, wherein dimethyl isosorbide is the hydrophilic excipient.

16. An adhesive coated sheet material comprising a flexible backing bearing on one surface thereof a formulation comprising a homogeneous mixture of

(i) a pressure sensitive adhesive;

(ii) a therapeutically effective amount of a nonsteroidal antiinflammatory drug selected from the group consisting of phenylpropionic acid derivatives and phenylacetic acid derivatives;

(iii) a lipophilic excipient selected from the group consisting of fatty acid alkyl esters and fatty acid monoglycerides; and

(iv) a hydrophilic excipient selected from the group consisting of polyethylene glycol, polyethylene glycol esters, isosorbide ethers, and diethylene glycol ethers.

17. A formulation according to Claim 16, wherein the lipophilic excipient is ethyl oleate, isopropyl palmitate, isopropyl myristate, or glycerol monolaurate.

18. A formulation according to Claim 16, wherein the nonsteroidal antiinflammatory drug has a solubility in the hydrophilic excipient of at least about 200 mg/g.

19. A formulation according to Claim 16, wherein the hydrophilic excipient is PEG 400, PEG 400 monolaurate, isosorbide dimethyl ether, diglyme, diethylene glycol diethyl ether, or diethylene glycol dibutyl ether.

20. A formulation according to Claim 16, wherein the lipophilic excipient is isopropyl myristate, ethyl oleate, or a combination thereof.

21. A formulation according to Claim 16, wherein dimethyl isosorbide is the hydrophilic excipient.

22. A formulation according to Claim 16, wherein the nonsteroidal antiinflammatory drug is flurbiprofen.

23. A method of treating in an animal a condition capable of treatment by a nonsteroidal antiinflammatory drug, comprising the steps of:

(i) providing a transdermal drug delivery formulation according to Claim 1;

(ii) applying the formulation to the skin of the animal; and

(iii) allowing the formulation to remain on the skin in order to establish or maintain a therapeutically effective blood level of the nonsteroidal antiinflammatory drug.

24. A topical and/or transdermal drug delivery formulation, comprising:

(i) a therapeutically effective amount of a nonsteroidal antiinflammatory drug selected from the group consisting of phenylpropionic acid derivatives and phenylacetic acid derivatives;

(ii) a lipophilic excipient selected from the group consisting of ethyl oleate, isopropyl myristate, and a mixture thereof; and

(iii) dimethylisosorbide,

wherein the lipophilic excipient and the dimethylisosorbide are miscible with one another in the amounts employed, and wherein the nonsteroidal antiinflammatory drug is substantially fully dissolved in the formulation.

25. A topical and/or transdermal drug delivery formulation, comprising:

(i) a therapeutically effective amount of a nonsteroidal antiinflammatory drug selected from the group consisting of phenylpropionic acid derivatives and phenylacetic acid derivatives;

(ii) a lipophilic excipient selected from the group consisting of fatty acid alkyl esters and fatty acid monoglycerides;

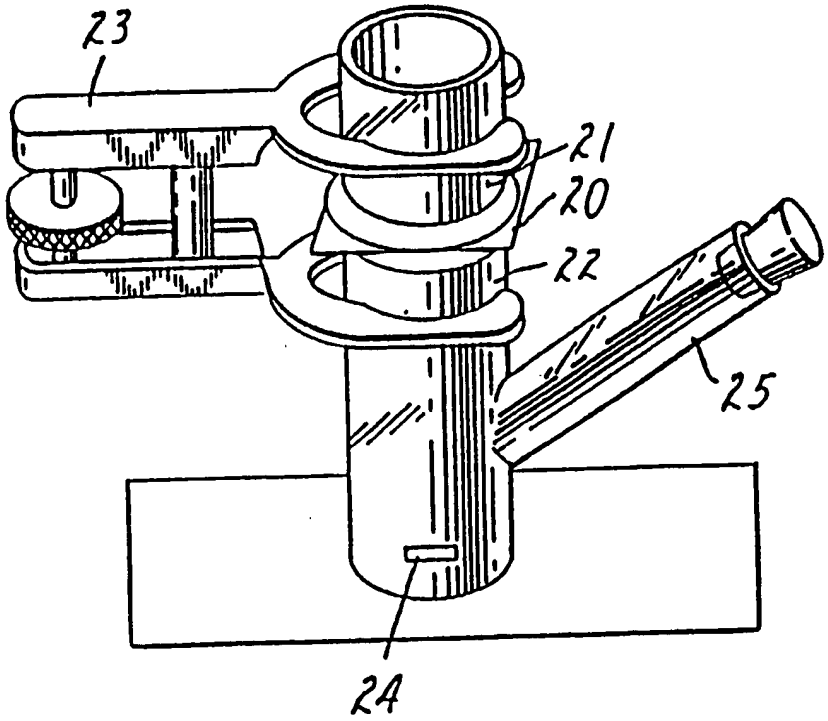
(iii) a hydrophilic excipient selected from the group consisting of polyethylene glycols, polyethylene glycol esters, isosorbide ethers, and diethylene glycol ethers; and

(iv) a pressure sensitive adhesive,

wherein the drug, the lipophilic excipient, and the hydrophilic excipient are substantially uniformly dispersed in the pressure sensitive adhesive.

26. A formulation according to Claim 25 wherein the nonsteroidal antiinflammatory drug is flurbiprofen.

27. A formulation according to Claim 25 wherein the nonsteroidal antiinflammatory drug is substantially fully dissolved in the formulation.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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/04156

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/19 A61K47/14 A61K47/10 A61K47/26 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP,A,0 206 291 (KLINGE-PHARMA GMBH) 30 December 1986 see claims 1,2,4	1,3,4,6, 11,12,23 10,14
X Y	EP,A,0 398 287 (MEDICE CHEM.-PHARM. FABRIK) 22 November 1990 see claims 1-5	1,4-8 10,14, 16-18, 20,22
X	EP,A,0 279 519 (THE BOOTS COMPANY PLC) 24 August 1988 see claims 1,5 see page 2, line 20 - page 3, line 14	1,4-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 1994	25.07.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/04156

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 091 964 (NITTO ELECTRIC INDUSTRIAL CO. LTD.) 26 October 1983 see page 2, line 26 - page 3, line 24 see page 4, line 25 - page 5, line 13 see page 7, paragraph 2 see page 8, paragraph 2	16-18, 20,22

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/04156

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Reamrk: Although claim 23 is directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of th e composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US 94/04156

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EP-A-0206291	30-12-86	DE-A-	3522550	02-01-87
		US-A-	4704406	03-11-87
EP-A-0398287	22-11-90	AU-A-	3987893	19-08-93
		AU-A-	5509190	22-11-90
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